Remarks

By this Amendment, the Title has been amended to be more specifically descriptive.

Claims 78-99 were pending in this application. Claims 78, 79, 82-89 and 98 are canceled without prejudice. Claims 80 and 90 are amended to incorporate the relevant limitations of canceled claims 78 and 82, respectively; claim 99 is amended to adjust the claim dependency in light of the cancellation of claim 98; and claims 91and 97 are amended for clarification. Support for these amendments can be found throughout the specification and original claims, such as at page 27, lines 31-32. Applicants reserve the right to pursue at a later date any subject matter removed from consideration by this amendment.

No new matter is introduced by the foregoing amendments. After entry of this Amendment, **claims 80, 81, 90-97 and 99 are pending in this application (of which claims 91 and 99 are currently withdrawn)**. Consideration and allowance of the pending claims is requested.

Restriction/Election

Applicants note that the Office has acknowledged the election of Group I, claims 78-97. However, this requirement has not been made final. Applicants note that the Office has maintained the asserted lack of unity between claims 78-97 and claims 98-99 by citing (for the first time in the pending action) U.S. Patent No. 6,080,750 (the '750 patent), which allegedly describes a compound that is "the core of" Applicants' compound of formula XV.

Without any admission as to the correctness of the Office's allegation that the '750 patent teaches any compound that implicates Applicants' invention, by this Amendment, claims reciting methods using compound XV (claims 78, 79, 82-89 and 98) have been canceled. The remaining claims (80, 81, 90-97 and 99) are **limited to methods using compositions comprising a compound of formula XV'**. Applicants submit that the generic compound described in the '750 patent does not encompass compound XV', and so cannot support the asserted lack of unity between the currently pending claims. Applicants respectfully request recombination of withdrawn claim 99.

Claim 91 is also currently withdrawn, being directed to non-elected species. Applicants understand that withdrawn claim 91 will be rejoined upon the allowance of a generic claim such as claim 90.

Rejection under 35 U.S.C. § 112, first paragraph (enablement)

Claims 78-82, 84-90 and 92-97 are rejected under 35 U.S.C. §112, first paragraph, for allegedly failing to comply with the enablement requirement. The Office asserts that the specification "lacks adequate guidance, direction or discussion to apprise the skilled artisan how the claimed compound may be used to achieve (1) the inhibition of GRP activity and (2) the disclosed utilities for treating conditions wherein GRP inhibition has been implicated" (Office action, at page 3). Solely to advance prosecution in this case, claims 78, 79, 82, 84-89 and 98 have been canceled without prejudice. Applicants traverse this rejection as applied to claims 80, 81 and 90-97, for the following reason(s).

Undue experimentation would not be required to use compound 77427 to inhibit GRP or treat a condition by inhibition of GRP

As set forth in the MPEP at §2164, the standard for determining whether a claimed invention is supported by an enabling description is whether one of skill in the art would be able to make or use the invention without "undue experimentation." The factors used to determine whether experimentation is "undue" are: 1) the quantity of experimentation n necessary, (2) the amount of guidance in the specification, (3) the presence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the level of skill in the art, (7) the predictability of the art, and (8) the breadth of the claims (*In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)). Applicants submit that when taken in light of the nature of the invention, the knowledge in the art and the abundant guidance in the specification, including the working examples presented therein, the specification would allow one of skill in the art to make and use the full scope of the claimed invention without "undue experimentation."

The Nature of the Invention

The Office notes that the subject invention relates to identification of modulatory agents of adrenomedullin and gastrin releasing peptide (GRP). However, Applicants' claimed invention is considerably more specific than the Office describes. While the specification refers to various "modulatory agents," and defines "modulate" as encompassing either stimulatory or inhibitory activity (page 5, lines 1-3), the pending claims are limited to methods related to inhibition of a GRP activity. Moreover, as amended, the pending claims are also limited to use of compositions comprising a specific compound of formula XV' (also referred to in the specification as compound 77427). As discussed herein, GRP has long been associated with a variety of biological activities and conditions. Applicants' claimed invention arose from the identification of compound 77427 as a specific GRP-inhibitor (which is thoroughly described in the specification). From this discovery, Applicants developed methods of using compound 77427 to inhibit a GRP activity (claims 80-81), including of treating a condition by inhibiting an activity of GRP in a subject in need of such treatment (claims 90-97 and 99).

The Knowledge in the Art

Even before Applicants' filed the instant application (and the documents from which it takes priority), GRP was a known 27 amino acid peptide hormone that had been associated with many biological processes, including cell proliferation, lung development, food intake, and control of blood pressure (Specification at page 1, lines 25-30; Cuttitta *et al., Nature*, 316:823-826, 1985; Sunday *et al., J Clin Invest,* 102:584-594, 1998; Merali *et al., Neuropeptides*, 33:376-386, 1999; and Ohki-Hamazaki *et al., Nature*, 390:165-169, 1997; each of which is of record in this file).

Also well known in the art were GRP neutralizing antibodies, which inhibit GRP activity by blocking GRP binding to its cellular receptor (*see* for example, Cuttitta *et al., Nature*, 316:823-826, 1985; of record). These antibodies have been used to block GRP activity in many different contexts. For example, GRP blocking antibodies have been used to decrease proliferation of several types of cancer cells including lung cancer (*Id.*), pancreatic cancer (Avis *et al., Molecular Carcinogenesis,* 8:214-220, 1993; of record), and squamous cell carcinoma (Lango *et al., Journal of the National Cancer Institute,* 94:375-383, 2002; of record). Another

exemplary use of GRP neutralizing antibodies has been to treat chronic lung disease in an animal model of brochopulmonary dysplasia (BPD) (Sunday *et al., The Journal of Clinical Investigation,* 102:584-594, 1998; of record).

Thus, the knowledge of GRP activity and the effects of its inhibition with a GRP functional antagonist (exemplified by a neutralizing antibody) were well established before the priority date of the instant application. Accordingly, one of skill in the art would understand and could reasonably predict (through sound scientific reasoning) that a GRP-inhibitory compound that functions in much the same manner as a GRP neutralizing antibody (such as compound 77427) will similarly inhibit GRP activity and provide a therapeutic benefit to subjects with GRP-stimulated conditions.

Guidance in the Specification

The specification describes with abundant detail the identification and characterization of compound 77427 as a GRP functional inhibitor. Compound 77427 was identified as a GRP functional inhibitor in a two-step screening process that selected for compounds that both interfered with binding of GRP to a GRP neutralizing antibody (page 17, lines 17-25) and modulated a GRP activity (in this case, inhibited GRP stimulation of intracellular Ca^{+2} and IP_3 release) (page 20, lines 3-10). Applicants further demonstrated the ability of compound 77427 to inhibit several other GRP activities including: cellular proliferation (page 36, line 24 to page 37, line 3), tumor growth (page 37, lines 4-14), *in vitro* angiogenesis (page 35, line 28 to page 36, line 10), and *in vivo* angiogenesis (page 36, lines 11-23). Thus, the specification both describes the identification of compound 77427 as a GRP inhibitor, and demonstrates its use in multiple examples of methods of inhibiting a GRP activity (including inhibition of GRP stimulation of intracellular levels of one or both of IP_3 or Ca^{+2}). Moreover, Applicants' working examples enable one of skill in the art to use compound 77427 in methods of treating a condition by inhibiting a GRP activity. Significantly, Applicants demonstrated that the inhibition of endothelial cell cord formation in matrigel (an *in vitro* assay of angiogenesis) by compound 77427 can be replicated in an *in vivo*, whole animal assay of angiogenesis (the directed *in vivo* angiogenesis assay) (page 35, line 28 to page 36, line 23). Likewise, the ability of compound 77427 to inhibit cellular proliferation in tumor cell cultures was also replicated in an *in* vivo,

whole animal xenograft model (page 36, line 24 to page 37, line 14). From these working examples, Applicants thus provide an objective showing to one of skill in the art that compound 77427 is useful to treat conditions related to aberrant angiogenesis, such as GRP-influenced cellular proliferation, and including the cancers recited in the claims.

The Office asserts that one of skill "would not accept . . . Applicants' statement that such an objective could be achieved in any type of cancer cell . . . without enabling a set of species representative of full scope of cancers known to the art" (Office action, at page 5). However, Applicants note that as discussed above, before the priority date of the instant application, inhibition of cellular proliferation of at least lung, pancreatic, and squamous cell cancers had been achieved using a GRP neutralizing antibody. Compound 77427 is a GRP functional antagonist that functions in much the same manner as the previously-known GRP neutralizing antibodies. Thus, one of skill in the art could reasonably predict that a therapeutic result achieved with a GRP neutralizing antibody could be similarly achieved with compound 77427. Indeed, as noted above, Applicants demonstrate an efficacy of compound 77427 analogous to the ability of the GRP blocking antibody to inhibit lung cancer cell proliferation and tumor development in a whole animal xenograft model.

Additionally, because of the knowledge in the art of the association between GRP and multiple distinct cancer types, one of skill in the art would predict (through sound scientific reasoning) the effective use of a composition comprising compound 77427 to inhibit cellular proliferation by inhibiting GRP activity in any cancer cell that expresses GRP and the GRP cellular receptor. Significantly, this prediction has been appreciated by the art subsequent to the priority date of the instant application in Patel *et al.*, *Biochim. et Biophys. Acta*, 1766:23-41, 2006 (submitted herein as **Exhibit A**). Exhibit A describes the knowledge in the art of the mitogenic role of GRP and lung, prostate, breast, gastric, pancreatic, and colorectal cancers. Significantly, Exhibit A suggests a significant therapeutic role for GRP-inhibitors such as compound 7742. Applicants' working examples also provide guidance to one of skill in the art for how to test the effect of compound 77427 on the cellular proliferation of any cancer cell type, both in the *in vitro* cell culture as well as *in vivo* whole animal contexts. Given the high level of skill in the art, testing a known compound to determine its effects on the proliferation of a cell

line using these known methods would not take excessive trial and error. Accordingly, in light of Applicants' teachings, any experimentation that might be necessary to test the ability of compound 77427 to inhibit cellular proliferation of a particular cancer type would not be undue.

Moreover, as discussed above, Applicants demonstrate both the previously-unknown angiogenic property of GRP as well as the corresponding ability of compound 77427 to inhibit angiogenesis. The connection between angiogenesis and cellular proliferation has long been known in the art (see *e.g.* Folkman *et al.*, *Nature*, 339:58-61, 1989, submitted herein as **Exhibit B**). Thus, one of skill in the art could reasonably predict that an inhibitor of angiogenesis (such as compound 77427) would also be an effective inhibitor of cellular proliferation.

Lastly, as described above, GRP is strongly associated with chronic lung disease (such as bronchopulmonary dysplasia (BPD)), regulation of food intake and regulation of blood pressure. Moreover, it has been shown that use of a GRP neutralizing antibody can decrease the severity of disease in a baboon model of BPD (Sunday *et al., J Clin Invest,* 102:584-594, 1998, of record); and that mice lacking a GRP-related cellular receptor have increased food intake and hypertension (Ohki-Hamazaki *et al., Nature*, 390:165-169, 1997, of record). Thus, one of skill in the art would reasonably predict that compound 77427, which Applicants demonstrate is a GRP functional antagonist, could be used to treat (non-elected) conditions such as BPD, an eating disorder in which stimulation of food intake is desirable, and hypotension.

Taking together, the prior knowledge of GRP and inhibitors of GRP activity, and the abundant guidance and working examples in the subject disclosure, one of skill in the art would be able to practice the full scope of the claimed invention (not limited to the elected species) without undue experimentation. Applicants respectfully request that the enablement rejection of claims 80, 81 and 90-97 be withdrawn.

Request for Rejoinder of Withdrawn Claims

Applicants submit that based on the foregoing arguments, one of skill in the art would be able to practice the invention described by generic claim 90 without undue experimentation. As generic claim 90 is in condition for allowance, Applicants request that the species in withdrawn

claim 91 be rejoined and examined at this time. As discussed above, Applicants continue to traverse the maintained unity of invention rejection, and request that claim 99 also be rejoined.

Conclusion

Based on the foregoing amendments and arguments, the pending claims are in condition for allowance, and notification to that effect is requested. If for any reason the Examiner believes that a telephone conference would expedite allowance of the claims, please telephone the undersigned at the telephone number listed below.

Respectfully submitted,

KLARQUIST SPARKMAN, LLP

One World Trade Center, Suite 1600
121 S.W. Salmon Street
Portland, Oregon 97204
Telephone: (503) 595-5300
Facsimile: (503) 595-5301

By /Michael D. Hammer/
Michael D. Hammer, Ph.D.
Registration No. 59,258